

1) Cover Sheet:

Title: Precise Coil Positioning in Navigated Transcranial Magnetic Stimulation (nTMS) Feasibility in Depression Patients Trial

Short Title: Confident Trial

Protocol Number: **MGS-2018-SS**

Date: November 26, 2018

Sponsor: Magstim, Inc. 9855 W. 78th St, Suite 12; 844-624-7846

Study Principal Investigator: *Lothar Krinke PhD, Magstim, Inc. 844-624-7846*

Research Site key individual: Nicole Krummel, Georgia Behavioral Health Professionals, TMS Operations Leader, 678-426-2930

2) Purpose and Background:

Objective: The objective of this study is to evaluate the feasibility of adding a navigational system to traditional repetitive Transcranial Magnetic Stimulation (rTMS, referred to in this application as nTMS) as a way to establish and maintain precise coil positioning (contact, rotation, and tilt) and consistent brain region targeting throughout a nTMS treatment session and in subsequent nTMS sessions. Success will be evaluated via data analysis of information captured during nTMS, which will evaluate coordinates, contact, rotation, and tilt parameters of the stimulation pulses delivered. The study will be conducted with patients who have been selected as traditional rTMS candidates and have met the criteria for rTMS, which includes, but is not limited to the following: Adults with Major Depressive Disorder (MDD) who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode. For the purposes of this study, nTMS is referring to the use of a navigation device in combination with delivery of traditional rTMS.

Aim 1: Determine the percentage of successful nTMS treatment sessions. A successful nTMS treatment session is defined as the following: 80% of the TMS pulse trains are delivered while the coil is within acceptance criteria measured by tracking the following parameters: coil deviations from digitally saved target location, which includes contact (mm), rotation ($^{\circ}$), and tilt ($^{\circ}$) parameters. The acceptance criteria are met with coil position at the time of pulse delivery as follows: coil rotation within $\pm 15^{\circ}$ of target; coil tilt within $\pm 15^{\circ}$ of target; in-plane deviation within $\pm 5\text{mm}$ of target; contact deviation within $\pm 2\text{mm}$ of target.

Aim 2: Determine Patient Health Questionnaire (PHQ-9) change measured weekly from baseline to after 30 sessions of nTMS, collect Patient comfort data, measure Operator confidence and collect coil position data for nTMS sessions to determine future product improvements and clinical studies.

The goal of this proposal is to establish nTMS as a means of precise administration of transcranial magnetic stimulation. Ultimately, data from this study will be used to design larger, comparative studies to establish superior efficacy profiles in the treatment of MDD.

Background: rTMS is an FDA-approved, non-invasive brain stimulation treatment for MDD that uses an electromagnet coil to deliver rapid magnetic pulses to a targeted area of the prefrontal cortex. The magnetic pulses induce a weak electrical current in the brain, stimulating neuronal activity. In the treatment of MDD, the electromagnetic coil is placed over the patient's head to stimulate the DLPFC region of the brain. While this stimulation location has been used for some time now, recent studies have shown that the focal magnetic fields produced by rTMS are affected by how the device coil is positioned during treatment^{3,9}. Therefore, it is becoming clear that positioning and maintaining the coil at the optimal rotation and angle in relation to the patient's scalp, and consistently treating the exact same place within the DLPFC region may be crucial for optimal rTMS efficacy.

Existing Literature: rTMS is used to successfully treat individuals with MDD. However, discrepancies exist in the effect sizes and variable outcomes between subjects.

Coil Location: Individual anatomical variability and inter-expert variability have been argued to be the two main sources of error during rTMS therapy⁶. Both of these hurdles can be overcome with the addition of a neuronavigation system to rTMS. In fact, the use of neuronavigation has been reported to decrease the variability of the results reported from rTMS therapy on depressed patients⁵. Further, variability in localizing

the DLPFC is significantly lower when the rTMS is conducted with a neuronavigational method^{11,9}. A direct comparison study of MRI-guided and fMRI-guided navigated rTMS compared to traditional rTMS revealed a significantly larger effect size in the population who went through neuronavigation¹². These data support the addition of neuronavigation to the standard rTMS treatment regimen.

Coil Orientation: Coil orientation is an important factor to take into account in order to increase the response rate to rTMS treatment⁸. Both brain gyrification¹⁵ conductivity anisotropy (which leads to certain current flow directions) (Opitz et al., 2011) play a role in the electrical field's dependence on coil orientation⁸. Therefore, even when the coil is precisely located on the defined treatment location, the optimum coil orientation to elicit a motor-evoked potential (MEP) can be different; this was exquisitely described by the work of Balslev and colleagues (2007) who assessed the effect of eight different coil orientations on MEPs¹. Even minor changes in coil placement can affect the motor-evoked potentials¹³; therefore, the coil positioning needs to be continuously checked for high accuracy by adjusting the coil position or orientation during the rTMS session as needed¹⁴.

Of particular relevance is the perpendicularity of the e-field to the cortex is essential for the effectiveness of the rTMS treatment¹⁰. There is an extensive body of research on how to optimize the effect of rTMS by maximizing the strength of the e-field as the coil is applied perpendicular to the treatment target and how accurate coil orientation can improve the treatment results^{3,9}. For example, targeting the DLPFC for MDD treatment has often shown optimal results with 45 degrees coil orientation relative to parasagittal plane². On a similar note, Opitz and colleagues emphasize the need for individualized target definition for rTMS, and argue that the sensitivity of coil orientation is dependent on the TMS site, that is, the more posterior the target, the more susceptible it will be to the changes in coil orientation.

Significance: Taken together, these data validate that different variables such as location and orientation of the coil need to be carefully considered to optimize the treatment for each individual patient. We argue that this level of mm accuracy and reproducibility can hardly be achieved without neuronavigation. The proposed work will confirm feasibility of use of nTMS to achieve precise and targeted stimulation outcomes. Such precise neuronavigation holds the future potential to optimize treatment outcomes for patients, resulting in improved effect-sizes, reproducibility, and consistency within and between patients. Such opportunity to improve consistency advances the field of rTMS by defining stimulation parameters and ensuring those parameters are met on a patient-by-patient basis, optimizing individualized treatment.

Justification for study involving humans: Humans are the best model for this investigation as rTMS is already used in patient populations and the addition of navigational ability to this treatment would represent a refinement to the treatment. Therefore, it is optimal to test the navigational device within the context of its therapeutic setting; this requires use of human subjects.

Magstim Transcranial Magnetic Stimulators were first approved for clinical use in 2008. The current Magstim device was FDA cleared in August 2018.

3) Subjects:

Number of subjects: 50 subjects are expected to be recruited to achieve successful completion of a total of 25 subjects.

Gender of Subjects: Men and women will be recruited in accordance with their demographic representation within Georgia for the treatment of MDD. No one will be excluded based on gender. Pregnant women will be excluded due to the lack of knowledge about the potential effects of the treatment on a fetus.

Age of Subjects: All subjects will be between 18-80 years of age. Minors are excluded from this study as minors have unique brain development patterns and activity and as such, a separate, minor-specific study would be conducted to evaluate this population.

Racial and Ethnic Origin: Recruitment is expected to be in alignment with the demographic distributions of race and ethnic origin in Georgia (the clinic sites). No one will be excluded from the study based on race or ethnic origin.

Inclusion Criteria: Diagnosis of medication-resistant MDD; Age 18 years or older; Normal findings in the medical history, physical, and neurological examination

Exclusion Criteria: History of seizure disorder; History of neuroleptic medications/prior use of neuroleptics; Presence of implanted medical pump, metal plate, or metal object in skull or eye; Pregnant women

Vulnerable Subjects: Vulnerable subjects are not included in this study.

Contraception: As the study is only over the course of five treatment sessions, it is unlikely that an individual will become pregnant and have knowledge that they have become pregnant. If an individual becomes pregnant and notifies study staff, they will be removed from the study.

4) Methods and Procedures:

Design: This study is a feasibility trial. Each participant will receive 30 sessions of 10Hz (4 seconds per cycle) rTMS over the left DLPFC. At the prescribing psychiatrist's discretion, patients may receive 20Hz (2 seconds per cycle). Both treatment protocols have the same number of pulses delivered per session. The rTMS interventions will be guided by a neuronavigation system (StimGuide TMS Navigation System, Magstim, Ltd. Carmarthenshire, UK) for navigation to the treatment location and to ensure consistent placement and orientation of the coil during and between each session. For the purpose of this protocol, these sessions are referred to as nTMS. Coil position data will be captured for sessions 6 through 30 to determine the primary outcome, which is Percentage of successful treatment sessions.

The primary outcome measure will be the percentage of successful nTMS treatment sessions pooled from sessions 6 through 30 for each study subject. A successful nTMS treatment session is defined as: 80% of the TMS pulse trains are delivered while the coil is within acceptance criteria measured by tracking the following parameters: coil deviations from digitally saved target location, which includes contact (mm), rotation ($^{\circ}$), and tilt ($^{\circ}$) parameters. The acceptance criteria are met with coil position at the time of pulse delivery as follows: coil rotation within $\pm 15^{\circ}$ of target; coil tilt within $\pm 15^{\circ}$ of target; in-plane deviation within $\pm 5\text{mm}$ of target; contact deviation within $\pm 2\text{mm}$ of target.

The secondary outcome measures are:

- Patient Health Questionnaire (PHQ-9) change from baseline (prior to the first day of treatment but not on the first day of treatment) to after 30 sessions of nTMS.
- Patient comfort measured on a scale from 1 to 5; with 1 being uncomfortable and 5 being extremely comfortable at the completion of the last nTMS session.
- Operator confidence on a scale of 1 to 5; 1 being not confident at all in using StimGuide to consistently find the treatment site and deliver therapy to 5 being very confident in using StimGuide to consistently find the treatment site and deliver therapy at the end of the study.

- Coil position for every pulse train for each patient's nTMS session 6 through 30.

Procedure: The participant will be placed comfortably in the treatment chair in the field of view of technology for optical tracking, which tracks items with reflective spheres. A head reference, which is a lightweight 3-inch plastic piece with 4 reflective spheres, will be placed on the right side of the participant's forehead via either a headband or adhesive electrodes. Anatomical registration of the participant's scalp landmarks will be conducted by gently placing the tip of a pointer tool, which is a lightweight plastic piece with 4 reflective spheres, onto the participant's nasion, left ear, and right ear.

Motor threshold (MT), the lowest stimulation intensity to elicit a muscular response, will be determined using a light hand-held MT coil. The position of the coil will be adjusted to find the motor hotspot. EMG electrodes will be placed on the right APB (Abductor Pollicis Brevis). The MT coil will be moved in a 1 cm grid-like fashion while delivering pulses. A TMS-induced motor evoked potential (MEP) will have an amplitude greater than 50 uV. The largest recorded amplitude pulse > 50 uV will be selected as the MT, and registered as a target in StimGuide. The power intensity will be lowered until the lowest intensity elicits 5 out of 10 consecutive pulses that elicit a MEP of at least 50 uV.

The MT and location of the motor hotspot will be saved in the StimGuide TMS navigation system with the corresponding power intensity. If using the Beam F3 method, a mark will be placed at the F3 location, and the coil will be placed at 45 degrees tangential to the head. The treatment site will be registered in StimGuide. If using the 5.5 cm (anterior to MT hotspot) method, StimGuide will guide the operator to the location, and the coil will be placed at 45 degrees tangential to the head. The treatment site will be registered in StimGuide.

For the subsequent sessions, nTMS treatment will be delivered using the saved information. The StimGuide TMS navigation system will inform the operator of any deviation in rotation and angle of the treatment coil, or displacement of the treatment coil while it is being placed onto the treatment site and during the entire session. Such real-time feedback will ensure accurate placement of the coil from session to session while simultaneously ensuring optimized coil angling within treatment sessions; together, such dynamic navigation will enable nimble, individualized treatment that increases the likelihood of success for nTMS.

Experiment versus Standard of Care: All of the stimulation treatment received as part of this protocol is part of the standard of care recommended for these participants. Only patients whose physicians have referred them to have rTMS will participate. Therefore, all study visits related to this project are also part of the standard care the patient would normally receive. The only portion of the care the participant will receive that is unique to the experimental portion of this protocol is combining the navigational component/device with the standard rTMS component for five of their rTMS treatment sessions. If a patient does not wish to participate in this study, they still will receive rTMS as recommended by their physician.

Frequency and Duration of Procedure: The initial appointment will last approximately 60 minutes; each subsequent appointment will last approximately 45 minutes. The initial appointment will take longer due to the additional effort to establish and save the navigational target to be used in subsequent appointments. All experimental procedures are conducted at the same clinic at which patients would receive their standard rTMS treatment; therefore, there is no change in location for participants whether they participate in the study or simply receive their standard care. The patients will complete a PHQ-9 prior to receiving the first nTMS.

session as baseline (prior to the first day of treatment but not on the first day of treatment) and weekly until after the last nTMS session has been completed.

Timeline: Patients will be recruited to participate in the study for 30 treatment sessions. It is anticipated that all enrollment activities will be concluded by May 15, 2019 with the analysis completion anticipated by the end of June 2019.

End of the study: After 30 nTMS treatments, the patient will have completed the study. The primary and secondary outcome measures will be analyzed after the last patient has completed 30 sessions, every patient completed the patient comfort survey and PHQ-9 assessment and every operator has completed the operator confidence survey. Patients may receive additional treatments in a continued access phase of the study. No additional study data will be collected during this phase.

Hazards: No procedures or situations related to this work are expected to be hazardous.

Sample Collection: There is no sample collection associated with this protocol.

Data: Information and clinical data collected as part of the study will be labeled with the subject's initials and a study number, which will be in a locked file cabinet in the locked in the study coordinator's office. The record linking the patient name to the study ID number will be kept indefinitely in a confidential manner. Only study staff will have access to the study information. All other data will be stored for six years and then be destroyed. Information related to neuronavigation and tms treatment will also be entered into a secure web-based computer database (Magstim Insight). Coil positional data is stored within Magstim StimGuide.

Data Storage and Confidentiality:

Patient identifiable information and clinical data collected as part of the study will be kept in the Magstim Insight ("Insight") platform. Insight is a secure, cloud based, patient data management system developed by The Magstim Company Ltd. Access to the Insight system is controlled using user credentials (username and password), while communication to the Insight system is encrypted using SSL. Access to the Insight platform will be controlled by the PI, or an authorized study coordinator granted access by the PI.

Each participant in the study will be assigned unique coded (non-patient identifiable) identifier which is stored as part of the patient record within the Insight platform. These unique identifiers will be used when registering the patients within the Magstim StimGuide ("StimGuide") system.

StimGuide will be used to store data relevant to the coils position during a treatment session, along with the coordinates of the participants motor threshold and treatment locations. StimGuide employs Microsoft Bitlocker technology to encrypt all data stored on its internal hard drive. Access to StimGuide also requires the use of standard user credentials (username, password).

Positional data shall be exported from StimGuide for analysis by Magstim, Inc. in order to determine the positional accuracy of the TMS coil for each treatment session. The exported data shall not contain any patient identifiable information as all data is associated with the unique coded identifiers as described previously.

Once the study is completed all access to the data stored within Insight shall be disabled. The data will be kept for a period of 6 years at which time it shall be securely deleted.

Participation in this study is completely voluntary. Each participant has the right to choose not to participate or to withdraw participation at any point in this study without affecting his/her health care or other services to which they are entitled.

Confidentiality:

The screening for ineligible candidates will be destroyed after the project's completion (12 months). The information relating to an enrolled subject's contact/personal details will be kept within the Insight platform.

Direct identifiers such as name, address, and telephone number will be maintained within the Insight platform and shall be kept for six years in accordance with HIPAA. If new information is obtained about safety during the course of this study, participants will be contacted for re-consent.

Data stored within StimGuide is anonymized by the use of code identifiers.

The clinical data will be stripped of all identifying information. This detail will be thoroughly covered during the consent process. Additional details on confidentiality have been covered in Sections 13

5) Potential Risks

Risk Category: Minimal Risk. The probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Potential Risks: The stimulation parameters for nTMS (traditional rTMS) are safe and have been used on many people to study the brain over recent decades. Most people do not find the stimulation painful, but occasionally strong contractions of scalp muscles can cause some discomfort and headache. If the patient finds the procedure too uncomfortable, they may discontinue at any time. Headaches usually go away promptly with nonprescription medication. The noise of the magnet may affect hearing, so earplugs are worn during nTMS. Magnetic stimulation will not be performed in people who have pacemakers, implanted pumps or stimulators, metal objects inside the eye or skull, or who have a history or risk of seizure. This study uses a stimulation protocol that has medical (FDA) clearance for the treatment of MDD and has been used for many research studies of various other conditions. The risk of inducing a seizure with nTMS is considered very low (less than 1%) and similar to the incidence of seizures associated with antidepressant medications. Safety studies using TMS in patients with neurological disorders have demonstrated no permanence. Risks to a fetus are not known and that information is made clear in the Patient Consent Form. It is expected that nTMS (the addition of a navigational system to rTMS) offers no additional risks to patients.

There are risks of stress, emotional distress, inconvenience, and possible loss of privacy and confidentiality associated with participating in a research study. There may be other risks that are currently unknown.

Protection Against Risks: These risks are expected to be reversible for the most part, with the exception of hearing damage (mitigated by the ear plugs), loss of confidentiality (mitigated with data management safeguards), and seizure (mitigated by exclusion criteria). Discomfort and headache can be treated with OTC medication. Personnel will be trained to monitor for risks and to remove individuals from the study for whom participation appears to be producing unexpected negative reactions.

6) Potential Benefits:

There is the possibility of nTMS directly improving symptoms related to medication-resistant MDD.

Improved consistency and optimization of treatment delivery is expected to provide reproducible outcomes with little variability, thus improving predictability of patient outcomes.

The knowledge gained in this proposed research could lead to an optimization of nTMS delivery and improved care of patients with medication-resistant MDD. In this case, improved quality of life could be expected with the successful and effective development of nTMS therapies.

7) Subject Identification, Recruitment, and Consent/Assent

Method of Subject Identification and Recruitment:

Patients already referred for routine rTMS treatment for MDD will be recruited (via referrals from physician) to instead receive nTMS for the first five treatment sessions, followed by standard rTMS for the remainder of their treatment period. Since the physician will speak to the potential subjects about the possibility of participating in the study during an appointment time that was already scheduled and in a room that is used for patient visits, this will be a private conversation. Since the physician is the person referring the patient to receive rTMS treatment, the physician is the best person to describe the option for inclusion of the navigational system as part of a research study. Following a description of the options, the study coordinator will have no further interaction with the patient about the study. Instead, to minimize undue influence, the study coordinator will meet with interested patients to review the details and obtain consent.

HIPAA: Since identifiable information will be gathered, HIPAA Authorization forms will be signed by each participant as part of their recruitment.

Process of Consent: The process of consent will take place at the clinic, following a standard appointment with the patient's physician. This process will occur in the clinic and no more 10 days prior to the first nTMS treatment. Subjects may take as much time as needed to consider participation in the study. The study staff will make every effort to meet with the potential subjects as many times as needed to clarify any portions of the consent form. The potential subject may take the consent form home with them and they will have a number provided to them to call the study staff if they are interested in participating or have follow-up questions. Any oral or written information will be provided to participants in their own language. Nicole Krummel is the authorized individual authorized to provide consent.

Subject Comprehension: Subjects will be encouraged to ask questions during the consenting process. Additionally, the study coordinator will ask the potential subjects if they have any questions and will attempt to assess their comprehension of the study by asking them to state their understanding of the research portion of the study prior to signing the consent form. The recruiting clinician will ensure that the subject themselves or

representatives of the subjects have sufficient knowledge and comprehension of all elements of the informed consent and are able to make an informed decision about participation

Documentation of Consent: Consent will be documented via signed informed consent forms. These forms will be maintained in a secure way that is accessible only to the study staff. The study PI, Lothar Krinke, is responsible for ensuring that valid consent is obtained and documented for all subjects.

Costs to Subject: All participants are receiving rTMS treatment as part of their standard of care. Therefore, there is no additional cost to them in terms of their time, transportation, or the addition of neuronavigation to the protocol.

Contact Information for Concerns:

This research is being overseen by Aspire Independent Review Board (“IRB”). An IRB is a group of people who perform independent review of research studies. You may talk to them at 1-877-366-5414 (toll free) if:

- ☐ You have questions, concerns, or complaints that are not being answered by the research team.
- ☐ You are not getting answers from the research team.
- ☐ You cannot reach the research team.
- ☐ You want to talk to someone else about the research.
- ☐ You have questions about your rights as a research subject.

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Withdrawal of Subjects: Any subject is free to withdraw from the study at any time.

Additionally, the investigator can remove a participant from the study at any time if she believes that continuing is not in his/her best medical interest, or if he/she is unable to comply with the requirements of the study.

Any subjects withdrawn or removed from the study will not be considered to have completed the study and therefore, no data from these individuals will be utilized in the evaluation of the results (except for the purposes of reporting an adverse event).

Sharing of Results with Subjects/Incidental Findings: Results will not be disseminated to participants.

However, all participants are receiving navigation as part of this study and therefore no “unblinding” would be needed/useful.

8) Consent Form

A consent form is attached for review.

9) Compensation of Subjects/Payment or Participation

Subjects are not compensated for their participation. In the event that this research activity results in an injury, treatment will be available, including first aid emergency treatment, and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to the subject or their insurance company. Any participant who thinks they have suffered a research related injury should notify the study coordinator right away. No commitment is made by the study site to provide free medical care or money for injuries to participants in this study.

10) Data and Confidentiality

Coil position data for every treatment session will be captured and stored in the study database. Only data from session 6 through 30 will be used to for the primary endpoint determination to allow for operators and patients to get used to the procedure during the first 10 sessions. PHQ-9 will be obtained from every patient prior to the first nTMS session and weekly until after the last session has been completed. The patient comfort survey will be administered after the last session has been completed. The operator survey will be administered after the last study patients has exited the study.

Statistical Plan: This is a pilot study and therefore, the data will be used to assess feasibility, adverse events, time, cost, etc. in an attempt to predict an appropriate sample size and optimize design prior to a larger-scale study.

Data Monitoring to Ensure Safety: This study is not considered greater than minimal risk.

Since the rTMS system is a 510(k)-cleared HORIZON system, any adverse event will be reported to MAUDE. When informed of an adverse event involving a cleared device in the US, Magstim will investigate and if , report the event in accordance with QP027 – Incident Reporting Procedure and the Medical Device Reporting (MDR) regulation (21 CFR 803). Furthermore, Magstim also has in place a Quality Procedure to initiate field corrections should this be required QP059 Field (Safety) Corrective Action Procedure. If an adverse event occurs related to the navigation system, a non-510(k)-cleared StimGuide, that adverse event will be reported via the IDE program.

Additionally, any serious adverse event, this will be reported to the IRB immediately (within 24 hours). Any recommendations will be implemented.

Data Storage and Confidentiality: Information and clinical data collected as part of the study will be labeled with participant initials and a study number; information (without the name) will be entered into a computer database and locked file cabinet in the study site coordinator, Nicole Krummel's office. The record linking the name to the MRN study ID number will be kept indefinitely at the MRN in a confidential manner in case the participant needs future access to their data. Only study staff will have access to the study information. All other data will be stored for six years and then be destroyed. Access to the data will be limited to the PIXXXX

Identification information and data collected from each participant will be entered into the Magstim Insight online data warehouse.

Data relating to the coils position during treatment is recorded by the Magstim StimGuide system.

Participation in this study is completely voluntary. Each participant has the right to choose not to participate or to withdraw participation at any point in this study without affecting his/her health care or other services to which they are entitled.

Confidentiality: The screening for ineligible candidates will be destroyed after the project's completion (12 months). The document containing contact/personal information for enrolled participants will be kept on a password-protected computer.

Direct identifiers such as name, address, and telephone number will be maintained in a password-protected computer in the locked office of the principal investigator and kept for six years in accordance with HIPAA. If new information is obtained about safety during the course of this study, participants will be contacted for re-consent.

The clinical data will be stripped of all identifying information. This detail will be thoroughly covered during the consent process.

Privacy of Subject: Potential subjects will be approached by research personnel in a private room in the clinic. They will be assured that only research personnel will have access to the information provided. All information provided will be maintained in a secured research area for which only study staff have access.

All nTMS appointments are conducted within the clinic. The door is kept closed during experiment appointments. Because normal rTMS treatments are also conducted at this clinic and the participants are already receiving those treatments as part of their standard of care, there would be no obvious indication that the individual is a part of the research study. All other standard privacy measures (associated with standard of care in the clinic) will be maintained.

11) Background and Experience of Investigators

PI CV/resume and Human Subjects Protection training certificate is attached

Research Staff: most current human subjects protection training certificate is attached.

The Principal Investigator: As PI in this project, Dr. Lothar Krinke PhD will be responsible for supervising and coordinating all aspects of the research. Dr. Krinke has the expertise and experience to perform this role well in the proposed research.

Research Coordinator: Nicole Krummel will serve as the research coordinator and will be responsible for the day-to-day coordination of the trial. Nicole will ensure compliance with regulatory and training requirements for any other research staff. She is experienced at recruiting research subjects and ensuring their confidential participation. The PI will directly oversee the research coordinator.

Study Staff:

Study Site: 2 Clinics: This facility contains all the TMS, rTMS and Neuronavigation devices necessary for successful completion of the study. It is also a private location ensuring subject privacy.

12) Instruments

Device data collection will be managed electronically as noted. Consent data and simple survey tools will be managed in accordance with confidentiality standards noted earlier in the document.

13) APPROVAL FORM FROM PARTICIPATING ORIGINATING INSTITUTIONS (where applicable)

Not applicable

14) Devices

Medical Devices: Please respond to all questions in this section.

A Horizon Performance System device and StimGuide TMS Neuronavigation System are used in the study (The Magstim Company Limited, Spring Gardens, Whitland, Carmarthenshire, SA34 0HR, UK).

Has an Investigational Device Exemption (IDE) application been submitted to the FDA?

No an IDE has not been submitted to the FDA

The device meets the requirements for an abbreviated IDE if all of the following are TRUE. Please articulate responses to all of the following:

*The device is not banned. **TRUE.*** The Horizon Performance System is FDA-approved for the treatment of medication-resistant depression under K180907.

*The device is not a significant risk device. **TRUE.*** Evidence-based guidelines have been published on the safe use of rTMS as a therapeutic device (Lefaucheur, et al., 2014)

*The sponsor or investigator will label the device in accordance with 21CFR812.5. **TRUE.*** The devices are labeled accordingly.

*The sponsor or investigator will comply with the requirements of 21CFR812.46 with respect to monitoring investigations. **TRUE.*** The investigator will comply with the requirements regarding monitoring of investigations.

*The sponsor or investigator will maintain research records required under 21CFR812.140 (b) and (5) and make the reports required under 21CFR812.150 (b) (1) through (3) and (5) through (10). **TRUE.*** The investigator will maintain research records as described.

*The sponsor or investigator will ensure that participating investigators maintain the records required by 21CFR812.140 (a)(3)(i) and make the reports required under 21CFR812.150(a) (1) (2) (5) and (7). **TRUE.*** The investigator will ensure that all study staff and investigators maintain records as described above.

*The sponsor or investigator will comply with the prohibitions in 21CFR812.7 against promotion and other practices. **TRUE.*** The investigator will comply with all prohibitions against promotion and other practices.

Please complete the section below to determine if an IDE is required:

Is the device FDA-approved for marketing and is it being used or investigated in accordance with its labeling.-

-The Horizon Performance System has been cleared by the FDA for the treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode.

-The StimGuide TMS Neuronavigation System is not cleared by the FDA.

Is the device a diagnostic device?

No.

Is the device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution?

No.

Is the device testing for the purpose of determining safety and effectiveness?

No. This is a feasibility study.

Is the device a custom device as defined in 21CFR812.3(b)?

No.

Provide a detailed description of device storage and accountability procedures:

Devices for the study will be sent from Magstim headquarters in Whitland, Wales to US Headquarters in White Bear Lake, MN only upon approval from the IRB.

Who will have access to the device?

The access to the device will be limited to the study staff who are trained in the safe operation of these devices.

What security safeguards are in place to ensure proper accountability, access, and storage of the device?

The devices are stored with the locked at the Georgia Behavioral Health office at Sandy Springs, 5775 Peachtree Dunwoody Road in Sandy Springs, Georgia, Suite 200, Atlanta, GA 30432. In addition to the security at the clinic, the specific room in which the devices are maintained is also locked when not in use. Only the study staff have access to the room. The PI assumes accountability for the devices and their proper use.

If the device is experimental, will it be labeled "Investigational Use Only"?

Yes.

Who will be responsible for:

Device accountability. The PI.

Labeling/dispensing. The PI.

State the qualifications of this person. CV Attached

Describe how the investigational device is controlled, and how accidental use outside of approved research will be avoided.

The equipment is locked in the clinic. Only the study staff have access to the locked rooms. The software program used to run the equipment is password protected.

Non-Significant Risk Determination Section

Is the device intended as an implant (≥ 30 days)?

No.

Is the device for use supporting or sustaining human life?

No.

Is the device for a use of substantial importance in diagnosing, curing, mitigating or treating disease or preventing impairment of human health?

No. This protocol is an exploratory study to determine whether coil positioning via nTMS can be achieved during and throughout treatment sessions.

Does the use of the device present a potential for serious risk to health, safety or welfare of the subjects?

The use of the device does not pose the potential for serious risk to health, safety or welfare of subjects. The protocol parameters are well within the bounds determined by the FDA for approval for the treatment of

depression and migraine. The only difference is the addition of a navigation system to optimize target localization and adherence.

Explain why the use of the device in this study poses non-significant risk, and attach any other supporting information. In addition, explain whether the sponsor, the FDA or any other oversight organization has already made a risk determination for the device.

The device poses a non-significant risk to participants given that the parameters used are well within the FDA-approved rTMS therapy for the treatment of depression. The exclusion and inclusion criteria also ensure an added level of safety in using this device.

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INFORMED CONSENT TO PARTICIPATE IN CLINICAL RESEARCH STUDY

Title: Precise Coil Positioning in Navigated Transcranial Magnetic Stimulation (nTMS) in Medication-Resistant Major Depressive Disorder (MDD): A Feasibility Study

Sponsor: Magstim, Inc.

Protocol Number: MGS-2018-SS

Principal Investigator: Dr. Lothar Krinke, PhD, Magstim, Inc.

Georgia Behavioral Health Professionals
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This is a research study. You are being asked to take part in this study because your physician has referred you for repetitive Transcranial Magnetic Stimulation (rTMS) as a treatment for Major Depressive Disorder (MDD). This study includes only individuals who voluntarily choose to participate. Please take your time to make your decision. Discuss it in confidence with your regular doctor, friends and family if you want. Be sure to ask questions about anything you do not understand in this document.

WHAT IS THIS STUDY ABOUT?

The purpose of this study is to evaluate the feasibility of adding a navigational system to traditional rTMS (referred to in the study as nTMS) to establish and maintain precise coil positioning (contact, rotation, and tilt) and consistent brain region targeting throughout a nTMS treatment session and in subsequent nTMS sessions. The study device is investigational, which means that it is not approved by the Food and Drug Administration (FDA).

This research is being done because there is evidence that variability in patient response to rTMS is due to inconsistent placement and positioning of the coil during treatment. Therefore, the goal of this research is to confirm that the addition of navigation to rTMS is feasible; this would aid in consistent application of the treatment.

If you participate in this study, you will receive navigation as part of your rTMS treatment (for 30 of your total treatments). Your rTMS treatment is standard of care. The navigation (nTMS) is the investigational procedure. Please ask the study staff if you have any questions about the difference.

FINANCIAL DISCLOSURE:

Dr. Krinke, the investigator, owns shares in the company and is the CEO. Please ask if you have any questions about this conflict of interest.

HOW LONG IS THIS STUDY? HOW MANY OTHER PEOPLE WILL BE IN THIS STUDY?

About 25 people will take part in this study. You will be in the study for about one week, which involves attendance at only your normal appointments. You will not need any additional appointments as a result of taking part in this research. The first appointment will take about an hour and the follow up sessions will take approximately 45 minutes.

WHAT IF NEW INFORMATION BECOMES AVAILABLE?

If new information in relation to the study device becomes available, that may be relevant to the purpose and safety of the study and your willingness to continue participation in this study, you will be informed by the study staff.

WHAT WILL HAPPEN DURING THE STUDY?

If you agree to take part in this research study, you will be required to sign this informed consent form before any procedures take place.

STUDY PROCEDURES:

During the screening and if you qualify and continue, during the study the following procedures will occur:

- Questions asked about how you are feeling and current medications and medical conditions
- Questions about your past health, possibly including requests for your medical records

The study doctor will talk to you and give you a list of the things you must do to participate, such as:

- Use of contraception by female participants during the five-treatment study period.
- Questions asked about how you are feeling and current medications and medical conditions

At your first appointment, the device will deliver pulses of stimulating energy on the left side of your head in order to stimulate a muscle twitch in your right hand. This will be repeated 10 times in order to accurately locate the best position for the treatment application on your scalp. The actual treatment position is forward of the motor stimulation location (in an area called the pre-frontal cortex which is altered in major depression). So, the coil will be moved forward to a position based on the motor spot for actual treatment once the optimal strength of impulse from the coil and precise location of the motor spot is determined and the treatment position is determined

This treatment position will then be saved in the navigation system and used for the this initial and the subsequent 29 appointments (a total of 30 of your treatments).

Please tell your regular health care providers and any emergency care providers that you are participating in this research study.

WHAT ARE THE RISKS AND DISCOMFORTS OF PARTICIPATING IN THIS STUDY?

The study device has been associated with the following side effects:

The stimulation parameters for nTMS (traditional rTMS) are safe and have been used on many people to study the brain over recent decades. Most people do not find the stimulation painful, but occasionally occasional side effects include:

- strong contractions of scalp muscles can cause some discomfort and headache.

Some patients have experienced dizziness and a tingling sensation. If you find the procedure too uncomfortable, you may discontinue at any time. Headaches usually go away promptly with nonprescription medication.

The noise of the magnet may affect hearing, so earplugs are worn during nTMS.

Magnetic stimulation will not be performed in people who have pacemakers, implanted pumps or stimulators, metal objects inside the eye or skull, or who have a history or risk of seizure. This study uses a stimulation protocol that has been previously used on patients. The risk of inducing a seizure with nTMS is considered very low (less than 1%) and similar to the incidence of seizures associated with antidepressant medications.

Safety studies using TMS in patients with neurological disorders have demonstrated no permanence.

Risks to a fetus are not known.

It is expected that nTMS (the addition of a navigational system to rTMS) offers no additional risks to patients.

There may be risks to being in this study that we cannot predict.

You should discuss these risks with the doctor. Many side effects go away shortly after the treatment stops the study drug is stopped. These risks are expected to be reversible for the most part, with the exception of hearing damage (prevented by the ear plugs), loss of confidentiality (safeguards are in place to protect your data), and seizure (you must inform the study doctor if you have any previous history of seizures).

Discomfort and headache can be treated with over-the-counter medication. Personnel will be trained to monitor for risks and to remove individuals from the study for whom participation appears to be producing unexpected negative reactions.

Side effects occurring during the trial can be treated by the study doctor, if this is deemed necessary. It is important that you inform the study doctor any unusual or unpleasant effects which you should feel.

Are there pregnancy risks?

If you are a woman who can get pregnant, you will be required to use adequate methods of birth control. If you are unsure of these methods, please discuss them with your study doctor. You cannot participate in this study if you are pregnant. Since no adequate and well-controlled studies of the study device in pregnant women have been performed you should not become pregnant while participating in this study. If you think you are pregnant during the study, you must tell the study coordinator immediately. Risks to a fetus from TMS are not known. It is suggested that female participants of child bearing age take contraception for the duration they are involved in the study, but such use will not be confirmed. If you become pregnant, you will have to leave the study.

For more information about risks and side effects, ask the study doctor.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. Information learned from this study may benefit others in the future.

There is the possibility of nTMS directly improving symptoms related to medication-resistant MDD.

Improved consistency and optimization of treatment delivery is expected to provide reproducible outcomes with little variability, thus improving predictability of patient outcomes.

The knowledge gained in this proposed research could lead to an optimization of nTMS delivery and improved care of patients with medication-resistant MDD. In this case, improved quality of life could be expected with the successful and effective development of nTMS therapies.

WHAT, IF ANY, ARE THE ALTERNATIVES TO PARTICIPATING IN THIS STUDY?

This study is not designed to diagnose, treat or prevent any disease. Your alternative is to not participate. If you choose not to participate in the study, you will still receive rTMS therapy (as

recommended by your physician); you simply will not receive the use of the navigational system during rTMS.

CONFIDENTIALITY

Your personal information will be kept confidential to the extent permitted by law. We cannot guarantee absolute confidentiality. By signing this document, you give permission to access your medical records, including after withdrawal, for data verification purposes.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as:

- The study staff and other researchers involved in the study
- Magstim or those who work for or represent Magstim
- The U.S. Food and Drug Administration (FDA)
- Aspire Independent Review Board (IRB)

The results from the study may be published for scientific purposes, but your identity will be kept confidential.

In the rare event that your information is required to be disclosed by law to another entity, privacy laws may not apply, and neither the Sponsor nor Aspire IRB can protect your information.

WHAT ARE THE COSTS?

There are no additional costs associated with being in this study. You are responsible for your regular health care while in this study. You will not have to pay for the use of the navigation device during your study visits.

INVESTIGATOR PAYMENT

The Principal Investigator is the CEO of Magstim, Inc. As CEO, he receives salary from Magstim. The study site will be receiving no payment for participation in the study. The study site coordinator will receive regular compensation from Georgia Behavioral Health professionals as due course for her role in the delivery of patient care during the study.

WILL YOU BE COMPENSATED DURING THE STUDY?

You will not be compensated for participating in and completing this research study.

WHAT HAPPENS IF YOU HAVE COMPLICATIONS OR ARE INJURED?

If you have serious side effects, complications or are injured because of participating in this study, please contact the study doctor promptly. If this research activity results in an injury, treatment will be available, including first aid emergency treatment, and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to you or your insurance company. No commitment is made by the study site to provide free medical care or money for injuries to participants in this study.

YOUR RIGHTS AS A RESEARCH SUBJECT

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular doctor first.

YOUR RESPONSIBILITIES AS A RESEARCH SUBJECT

You will be asked to adhere to all instructions issued by the study doctor and other study staff. Furthermore, you should answer all asked questions truthfully.

Should you not comply with instructions, the study doctor may stop your study participation. Your study doctor may also exclude you from this trial if he/she deems it beneficial for your health, or if you do not meet the study requirements. Your participation in this study may be ended if the Sponsor stops the study for any reason.

WHOM TO CALL IF YOU HAVE QUESTIONS

For questions, concerns or complaints or information about the study or a research-related injury, contact the study doctor at the number on page 1.

This research is being overseen by Aspire Independent Review Board (“IRB”). An IRB is a group of people who perform independent review of research studies. You may talk to them at 1-877-366-5414 (toll free) if:

- You have questions, concerns, or complaints that are not being answered by the research team.
- You are not getting answers from the research team.
- You cannot reach the research team.
- You want to talk to someone else about the research.
- You have questions about your rights as a research subject.

Although Aspire IRB has approved the information provided in this informed consent form and has granted approval for the investigator to conduct the study this does not mean Aspire has approved your being part of the study. You need to read the information in this informed consent form for yourself and decide whether or not you want to be in this study.

SIGNATURE AND CONSENT TO BE IN THE STUDY

Your signature below means that you have read the above information about this study and have had a chance to ask questions to help you understand what you will be expected to do and that you agree to participate in this study. Your signature also means that you have had all your questions answered to your satisfaction and that you have been told that you can change your mind later if you want to. You will be given a signed and dated copy of this agreement. By signing this consent form, you are not giving up any of your legal rights.

_____/_____
 SIGNATURE OF SUBJECT DATE

PRINTED NAME OF SUBJECT

I confirm that a copy of this consent form has been given to this person to read and that this person has been told about the study. The contents of the consent form describing the study has been discussed with this person and I have made every effort to answer all questions to his or her satisfaction. I have watched this person sign the consent form.

_____/_____
 SIGNATURE OF PERSON OBTAINING CONSENT DATE

PRINTED NAME OF PERSON OBTAINING CONSENT

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